Attorney Docket: YOR920000779US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application

Applicant(s): B.D. Silverman
Docket No.: YOR920000779US2
Serial No.: 09/818,461
Filing Date: March 27, 2001
Group: 1631
Examiner: Michael L. Borin

I hereby certify that this paper is being deposited on this date with the U.S. Postal Service as first class mail addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Signature: Date: October 20, 2004

Title: Spatial Profiling of Proteins Using Hydrophobic Moments

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TRANSMITTAL OF APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith are the following documents relating to the above-identified patent application:

1. Appeal Brief (original and two copies); and
2. Copy of Notice of Appeal, filed on August 23, 2004, with copy of stamped return postcard indicating receipt of Notice by PTO on August 26, 2004.

There is an additional fee of $340 due in conjunction with this submission under 37 CFR §1.17(c). Please charge **IBM Corporation's Deposit Account No. 50-0510** the amount of $340 to cover this fee. In the event of non-payment or improper payment of a required fee, the Commissioner is authorized to charge or to credit **IBM Corporation's Deposit Account No. 50-0510** as required to correct the error. Duplicate copies of this letter and two copies of the Appeal Brief are enclosed.

Respectfully,

Date: October 20, 2004

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APPEAL BRIEF

Mail Stop Appeal Brief - Patents
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Alexandria, VA 22313-1450

Sir:

Appellant hereby appeal the final rejection dated June 8, 2004, of claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38 of the above-identified patent application.

REAL PARTY IN INTEREST

The present application is assigned to International Business Machines Corporation, as evidenced by an assignment recorded on March 27, 2001 in the United States Patent and Trademark Office at Reel 011676, Frame 0150. The assignee, International Business Machines Corporation, is the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are no known related appeals and interferences.

STATUS OF CLAIMS

The present application was filed on March 27, 2001 (claiming priority from United States Provisional Application Number 60/245,396, filed November 2, 2000) with claims 1-43. Claims 7-21, 28-32 and 39-43 have been withdrawn from consideration in response to a restriction requirement and claims 4, 25 and 36 have been withdrawn from consideration in response to a species election. Claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38 stand finally rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claims 1-3, 5 and 6 stand finally rejected under 35 U.S.C. §101 as allegedly drawn to non-statutory subject matter. Claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38 stand finally rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Claim 1 stands finally rejected 35 U.S.C. §102(b) as allegedly unpatentable over Bar-Or et al., Database CaPlus, DN 103:84898, Archives of Microbiology (1985), 142(1), pages 21-27 (hereinafter "Bar-Or"). No claims have been allowed.

STATUS OF AMENDMENTS

There has been no amendment filed subsequent to the final rejection. However, a Response to Final Rejection was filed on June 28, 2004 and a Notice of Appeal was filed on August 23, 2004.

SUMMARY OF INVENTION

The present invention provides techniques for spatially profiling proteins using hydrophobic moments (Specification, page 1, line 9).

The present invention provides a tool for probing protein structure (Specification, page 4, line 14). The present invention may be used to analyze any protein, but is particularly useful for analyzing proteins that form in an aqueous environment, such as globular proteins (Specification, page 4, lines 16-18). Because globular proteins form in an aqueous environment, they have a hydrophobic core and a hydrophilic exterior (Specification, page 4, lines 23-24). A hydrophobicity scale can be used to determine the hydrophobicity distribution of a protein

(Specification, page 4, lines 24-25). The resultant hydrophobicity distribution can be shifted and normalized, which places each protein with mathematical basis for comparison (Specification, page 4, line 26, through page 5, line 1). Without shifting the hydrophobicity distribution, the ability to compare different proteins is significantly degraded (Specification, page 5, lines 1-2).

ISSUES PRESENTED FOR REVIEW

i. Whether claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38 are properly rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention;

ii. Whether claims 1-3, 5 and 6 are properly rejected under 35 U.S.C. §101 as being allegedly drawn to non-statutory subject matter;

iii. Whether claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38 are properly rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement; and

iv. Whether claim 1 is properly rejected under 35 U.S.C. §102(b) as allegedly unpatentable over Bar-Or.

GROUPING OF CLAIMS

For purposes of the prior art rejection, independent claim 1, the only pending rejected claim, stands or falls alone.

ARGUMENT

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, in the final Office Action at page 2, 4th paragraph, the Examiner stated that,

> Claims 1, 22, 33, and claims dependent therefrom, recite the step of determining [a] hydrophobicity distribution of a protein, which is vague and indefinite. It is not clear whether, the distribution of protein addressed in the

> claim is in some physical environment, virtual environment, or, as it seems from the specification, is not a distribution of protein at all, but distribution of hydrophobicity throughout the given protein molecule.

There seems to be an unfounded level of confusion surrounding the term "hydrophobicity distribution of a protein." For example, the Examiner further stated in the final Office Action at page 3, 1st paragraph, that,

> Applicant explains that the hydrophobicity distribution is determined from the spatial distribution of amino acid residues. This may explain the term hydrophobicity distribution of amino acid residues in protein, but not the 'hydrophobicity distribution of a protein' as used in the claims.

Despite the Examiner's above assertions, Appellant respectfully maintains that the term "hydrophobicity distribution of a protein" is defined in the specification in such a way that the metes and bounds of the present claims are clearly ascertainable. By way of example only, the specification at page 4, lines 24-25, recites that a hydrophobicity scale can be used to determine the hydrophobicity distribution of a protein. For example, a hydrophobicity scale, such as that shown in FIG. 2, can be used to assign individual hydrophobicity values for each amino acid residue making up the protein. Thus, the "hydrophobicity distribution" arises from the spatial distribution of the amino acid residues, throughout the protein structure, and their assigned values of hydrophobicity. See, for example, page 9, lines 1-5 of the specification and FIG. 2.

Appellant further submits that the alleged discrepancy between the terms "hydrophobicity distribution of amino acid residues in a protein" (as set forth by the Examiner, see above) and "the hydrophobicity distribution of a protein" (as recited, e.g., in claims 1, 22 and 33) is a mere matter of preference. The Examiner is reminded that the "focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. . . . [Claims should be allowed] which define the patentable subject matter with a reasonable degree of particularity and

distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire." M.P.E.P. §2173.02 (emphasis in original)

The Examiner further stated in the final Office Action, at page 3, 1st paragraph, again in reference to the term "hydrophobicity distribution of a protein," that,

> the section in [the] specification addressed by applicant, describes values of hydrophobicity of amino acid residues lying within [a] certain surface, not 'hydrophobicity distribution of a protein.'"

Respectfully, it appears the Examiner has misunderstood the teachings of the present specification. The Examiner is referring to Appellant's prior reference to page 9, lines 1-5 of the specification. Namely, the paragraph spanning pages 8 and 9 of the specification (beginning on page 8, line 26) recites that an ellipsoidal surface is obtained and the values of hydrophobicity for amino acid residues lying within this surface are collected. This teaching is directed to spatially profiling the hydrophobicity distribution of amino acid residues in a protein using second-order moments. See, for example, page 8, lines 6-7 of the specification.

What Appellant in fact intended in making reference to page 9, lines 1-5 of the specification and FIG. 2 was simply that assigning values of hydrophobicity for the amino acid residues making up a protein may be based on consensus hydrophobicity values, such as those shown in FIG. 2. For example, the specification beginning on page 6, line 25, sets forth that the hydrophobicity distribution is determined wherein each amino acid residue is assigned a hydrophobicity consensus value, e.g., based on the representative hydrophobicity value table shown in FIG. 2.

In the Advisory Action dated July 20, 2004, the Examiner further stated that,

> it is noted that Fig. 2 cited by applicant illustrates hydrophobicities of particular amino acid residues, not 'hydrophobicity distribution of protein,' the latter term being related to, in a particular embodiment, by a hydrophobicity scale, but remaining vague in general.

The Examiner's above statement is somewhat unclear. However, as presented above, the specification clearly sets forth that FIG. 2 is an exemplary scale listing consensus

hydrophobicity values for 20 amino acid residues. As such, the table in FIG. 2 can be used to assign individual hydrophobicity values for the amino acid residues making up a protein. The spatial distribution of these amino acid residues throughout the protein structure and their assigned values of hydrophobicity can be used to determine the "hydrophobicity distribution of the protein."

Therefore, Appellant respectfully submits that the step of determining a hydrophobicity distribution of a protein is neither vague nor indefinite, given the teachings of the claims and supporting specification. As such, Appellant respectfully requests reconsideration and withdrawal of the rejections of claims 1, 22 and 33, as well as all claims dependent thereon.

Rejections under 35 U.S.C. §101

Claims 1-3, 5 and 6 are rejected under 35 U.S.C. §101 as being allegedly drawn to non-statutory subject matter. In the final Office Action, page 3, 2nd paragraph, the Examiner stated that,

> the listed instant claims are drawn to computation or manipulation of data or abstract information and as such is non-statutory subject matter due to being drawn to a non-tangible mathematical invention. No production or change in actual material is seen in the instant claims and thus is deemed non-statutory subject matter.

Appellant respectfully disagree with the Examiner's assertions. A process that is limited to a practical application of an abstract idea or mathematical algorithm in the technological arts is patentable. See Examination Guidelines for Computer-Related Inventions, § IV. B. 2. b. (ii). Independent claim 1, from which claims 2, 3, 5 and 6 ultimately depend, is expressly directed to a practical method for "spatially profiling proteins." Thus, these claims are clearly tied to a practical application.

In any event, the analysis does not stop there. The Supreme Court has stated that the "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to patentability of a process claim." Gottshalk v. Benson, 409 U.S. 63, 70, 175 U.S.P.Q. (BNA) 676 (1972). In other words, claims that require some kind of transformation of subject matter, which has been held to include intangible subject matter, such as data or signals, that are representative

of or constitute physical activity or objects have been held to comply with §101. See, for example, In re Warmerdam, 31 U.S.P.Q.2d (BNA) 1754, 1759 n.5 (Fed. Cir. 1994) or In re Schrader, 22 F.3d 290, 295, 30 U.S.P.Q.2d (BNA) 1455, 1459 n.12 (Fed. Cir. 1994). Thus, as expressly set forth in independent claim 1, a hydrophobicity distribution of a protein is determined. The hydrophobicity distribution is then *transformed* by being shifted.

Further, Appellant respectfully submits that by the hydrophobicity distribution being shifted, a useful, concrete and tangible result is produced. For example, the shifted hydrophobicity distribution may be used in comparing the hydrophobic moment profiles of different proteins and provide a basis for comparing hydrophobic ratios. See, for example, page 9, lines 15-19, of the specification. As highlighted in the specification, page 5, lines 1-2, without this shifting of the hydrophobicity distribution, the ability to compare different proteins would be significantly degraded.

As such, Appellant submits that claims 1-3, 5 and 6 comport with the requirements of 35 U.S.C. §101 and respectfully requests withdrawal of the rejection of claims 1-3, 5 and 6 under 35 U.S.C. §101.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Namely, the Examiner in the final Office Action, beginning at page 3, 3rd paragraph, stated that,

> the specification while being enabling for a computer-driven computational method made on a protein modeled in virtual environment, does not reasonably provide enablement for a method of profiling proteins by physically changing protein's hydrophobicity in a real environment.
>
> Applicant correctly reflects Examiner position that the claims seem to encompass not only computer-generated shifting in hydrophobicity but also physical processes.

The above rejection reflects a fundamental misunderstanding of the present teachings and of Appellant's previous response. First, Appellant has never indicated that the

present teachings are directed, in any way, to physically changing a protein's hydrophobicity. For example, at page 16, line 29, through page 17, line 1, of Appellant's response dated March 30, 2004, it was stated that,

> The overall teachings of the specification and claims. . . do not teach or suggest, e.g., physically shifting the hydrophobicity distribution of a protein. (emphasis added)

As described above and in the present specification, e.g., beginning on page 4, line 26, the hydrophobicity distribution is shifted in order to allow different proteins to be compared. Further, the specification at page 9, lines 5-8, in reference to shifting the hydrophobicity distribution, describes that,

> [t]he distribution of amino acid hydrophobicity is . . . shifted . . . such that the net hydrophobicity of each protein vanishes. This is done by subtracting the average hydrophobicity from each value in the hydrophobicity distribution.

Appellant further points out that M.P.E.P. §2164.08 indicates that "[w]hen analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification." (emphasis added) Thus, to assert that certain hypothetical embodiments are not enabled by the specification ignores the overall teachings of the specification and claims which do not teach or suggest, e.g., physically shifting the hydrophobicity distribution of a protein. Further, one of ordinary skill in the art would not contemplate such derivations of the present teachings, as it is not apparent, if at all possible, how one might go about physically shifting the hydrophobicity distribution of a protein. Thus, Appellant respectfully maintains that the present specification clearly enables the scope of the claims to which Appellant is entitled and respectfully requests withdrawal of the rejection under 35 U.S.C. §112, first paragraph, of claims 1-3, 5, 6, 22-24, 26, 27, 33-35, 37 and 38.

Prior art rejections

Claim 1 is rejected under 35 U.S.C. §102(b) as allegedly unpatentable over Bar-Or.

In the final Office Action at page 4, 4th paragraph, the Examiner stated that,

> Applicant argues that . . . [Bar-Or] is different as it teaches changing cell-surface properties. However . . . the Examiner interprets the claim as encompassing physical, not only computer-generated, changes in hydrophobicity. To this end, the referenced method includes initial evaluation of hydrophobicity, which reads on instantly claimed step of 'determining a hydrophobicity distribution,' and a step of treatment of cell surface which clearly shifts hydrophobicity distribution of a protein (e.g., as a result of treatment with a proteolytic agent).

As provided above, the present teachings are not, in any way, directed to physically changing a protein's hydrophobicity. The claims and specification clearly support this position. Thus, one of ordinary skill in the art should have no basis to interpret the claims as "encompassing physical changes in hydrophobicity." Therefore, the rejections over Bar-Or are baseless, as Bar-Or does not teach or suggest any elements of the present claims.

Specifically, Bar-Or is directed to experimentally shifting cell-surface hydrophobicity to hydrophilicity. See, for example, Bar-Or, Abstract. Bar-Or does not teach or suggest determining a hydrophobicity distribution of a protein. The techniques mentioned in Bar-Or are directed to shifting cell surface hydrophobicity. The distribution of hydrophobicity in a protein is not taught in Bar-Or.

Further, Bar-Or does not teach or suggest shifting the hydrophobicity distribution of a protein. What Bar-Or teaches is "releasing large amts. of protein . . . from the cell wall." Bar-Or, Abstract. This teaching is not at all related to shifting the hydrophobicity distribution of a protein. As such, Bar-Or does not teach or suggest any protein profiling techniques.

Therefore claim 1, is clearly patentable over Bar-Or.

The attention of the Examiner and the Appeal Board to this matter is appreciated.

Respectfully,

Date: October 20, 2004

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APPENDIX

1. (Original) A method for spatially profiling proteins, the method comprising the steps of:

determining a hydrophobicity distribution of a protein; and

shifting the hydrophobicity distribution.

2. (Original) The method of claim 1, wherein the step of shifting the hydrophobicity distribution comprises the step of shifting the hydrophobicity distribution such that a total hydrophobicity of the protein is zero.

3. (Original) The method of claim 2, further comprising the step of normalizing the shifted hydrophobicity distribution, thereby causing a standard deviation of the shifted hydrophobicity distribution to be unity.

4. (Withdrawn) The method of claim 3, further comprising the steps of:

determining, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

determining a profile of the adjusted zero-order moment of hydrophobicity;

determining a first distance of a maximum peak of a profile of the adjusted zero-order moment of hydrophobicity;

determining a second distance at which the adjusted zero-order moment of hydrophobicity vanishes; and

determining a ratio between the first and second distances.

5. (Original) The method of claim 3, further comprising the steps of:

determining, by using the shifted and normalized hydrophobicity distribution, an adjusted second-order moment of hydrophobicity;

determining a profile of the adjusted second-order moment of hydrophobicity;

determining a first distance at which a maximum peak of the profile of the adjusted second-order moment of hydrophobicity occurs;

determining, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

determining a second distance at which the adjusted zero-order moment of hydrophobicity vanishes; and

determining a ratio between the first and second distances.

6. (Original) The method of claim 1, wherein the step of determining a hydrophobicity distribution of a protein comprises the step of assigning a hydrophobicity value to each of a plurality of residues of the protein.

7. (Withdrawn) A method for spatially profiling proteins, the method comprising the steps of:

a) determining a shifted and normalized hydrophobicity distribution for a protein;

b) determining a centroid of the protein;

c) determining, by using the shifted and normalized hydrophobicity distribution, an adjusted second-order moment of hydrophobicity; and

d) determining a profile of the adjusted second-order moment of hydrophobicity.

8. (Withdrawn) The method of claim 7, wherein:

the step of determining a shifted and normalized hydrophobicity distribution comprises the steps of:

I) determining a residue center for each of a plurality of residues of the protein;

II) assigning each residue a hydrophobicity value, where a hydrophobicity value is assigned to a corresponding one of the residue centers;

III) shifting each the hydrophobicity values of the hydrophobicity distribution such that a total hydrophobicity of the protein is zero; and

IV) normalizing each of the hydrophobicity values, wherein the hydrophobicity distribution comprises the shifted and normalized hydrophobicity values, which thereby causes a standard deviation of the hydrophobicity distribution to be unity.

9. (Withdrawn) The method of claim 7, wherein the step of determining a profile of the adjusted second-order moment of hydrophobicity comprises the step of determining a first distance from the centroid at which the adjusted second-order moment of hydrophobicity is zero.

10. (Withdrawn) The method of claim 9, further comprising the steps of:

e) determining, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

f) determining a second distance from the centroid at which the adjusted zero-order moment of hydrophobicity is zero; and

g) determining a ratio between the first distance and the second distance.

11. (Withdrawn) The method of claim 10, wherein:

the step of a determining a first distance from the centroid at which the adjusted second-order moment of hydrophobicity is zero comprises the step of determining a surface enclosing an interior volume wherein any larger of a surface will yield a negative adjusted second-order moment of hydrophobicity; and

the step of determining a second distance from the centroid at which the adjusted zero-order moment of hydrophobicity is zero comprises the step of increasing the volume enclosed by the surface until the net hydrophobicity of the protein is zero.

12. (Withdrawn) The method of claim 11, wherein the surface is chosen from the group consisting of an ellipsoid and a sphere.

13. (Withdrawn) The method of claim 10, wherein both the first and second distances describe a surface.

14. (Withdrawn) The method of claim 13, wherein the surface is chosen from the group consisting of an ellipsoid and a sphere.

15. (Withdrawn) The method of claim 7, wherein the step of profiling an adjusted second-order moment of hydrophobicity further comprises the step of determining a profile of the adjusted second-order moment of hydrophobicity with distance from the centroid.

16. (Withdrawn) The method of claim 7, wherein the step of determining a centroid of the protein comprises the steps of:

I) determining a residue center for each of a plurality of residues of the protein;

II) assigning each of the residue centers a mass value of one; and

III) determining a center of mass of the protein by using the residue centers and the mass value of one at each residue centroid.

17. (Withdrawn) The method of claim 16, wherein the step of determining a residue center comprises, for each residue in the protein:

A) determining a location of each atom in the residue;

B) assigning a mass value of one to each location; and

C) determining a center of mass of the residue by using the locations of each atom and the mass value of one at each location;

18. (Withdrawn) The method of claim 16, wherein the step of determining a residue center comprises, for each residue in the protein, determining an alpha carbon atom location.

19. (Withdrawn) A method for spatially profiling proteins, the method comprising the steps of:

determining a shifted and normalized hydrophobicity distribution for a protein;

determining a centroid of the protein;

selecting a surface; and

calculating, by using the surface, a moment of the shifted and normalized hydrophobicity distribution.

20. (Withdrawn) The method of claim 19., wherein the moment is selected from the group consisting of a zero-order moment and a second-order moment.

21. (Withdrawn) The method of claim 19, wherein the surface is selected from the group consisting of a sphere and an ellipse.

22. (Original) A system comprising:

a memory that stores computer-readable code; and

a processor operatively coupled to the memory, the processor configured to implement the computer-readable code, the computer-readable code configured to:

determine a hydrophobicity distribution of a protein; and

shift the hydrophobicity distribution.

23. (Original) The system of claim 22, wherein the computer-readable code is further configured, when shifting the hydrophobicity distribution, to shift the hydrophobicity distribution such that a total hydrophobicity of the protein is zero.

24. (Original) The system of claim 23, wherein the computer-readable code is further configured to normalize the shifted hydrophobicity distribution, thereby causing a standard deviation of the shifted hydrophobicity distribution to be unity.

25. (Withdrawn) The system of claim 24, wherein the computer-readable code is further configured to:

determine, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

determine a profile of the adjusted zero-order moment of hydrophobicity;

determine a first distance of a maximum peak of a profile of the adjusted zero-order moment of hydrophobicity;

determine a second distance at which the adjusted zero-order moment of hydrophobicity vanishes; and

determine a ratio between the first and second distances.

26. (Original) The system of claim 24, wherein the computer-readable code is further configured to:

determine, by using the shifted and normalized hydrophobicity distribution, an adjusted second-order moment of hydrophobicity;

determine a profile of the adjusted second-order moment of hydrophobicity;

determine a first distance at which a maximum peak of the profile of the adjusted second-order moment of hydrophobicity occurs;

determine, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

determine a second distance at which the adjusted zero-order moment of hydrophobicity vanishes; and

determine a ratio between the first and second distances.

27. (Original) The system of claim 22, wherein the computer-readable code is further configured, when determining a hydrophobicity distribution of a protein, to assign a hydrophobicity value to each of a plurality of residues of the protein.

28. (Withdrawn) A system for spatially profiling proteins, comprising:

a memory that stores computer-readable code; and

a processor operatively coupled to the memory, the processor configured to implement the computer-readable code, the computer-readable code configured to:

a) determine a shifted and normalized hydrophobicity distribution for a protein;

b) determine a centroid of the protein;

c) determine, by using the shifted and normalized hydrophobicity distribution, an adjusted second-order moment of hydrophobicity; and

d) determine a profile of the adjusted second-order moment of hydrophobicity.

29. (Withdrawn) The system of claim 28, wherein the computer-readable code is further configured, when determining a profile of the adjusted second-order moment of hydrophobicity, to determine a first distance from the centroid at which the adjusted second-order moment of hydrophobicity is zero.

30. (Withdrawn) The system of claim 29, wherein the computer-readable code is further configured to:

e) determine, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

f) determine a second distance from the centroid at which the adjusted zero-order moment of hydrophobicity is zero; and

g) determine a ratio between the first distance and the second distance.

31. (Withdrawn) The system of claim 30, wherein:

the computer-readable code is further configured, when determining a first distance from the centroid at which the adjusted second-order moment of hydrophobicity is zero, to determine a surface enclosing an interior volume wherein any larger of a surface will yield a negative adjusted second-order moment of hydrophobicity; and

the computer-readable code is further configured, when determining a second distance from the centroid at which the adjusted zero-order moment of hydrophobicity is zero, to increase the volume enclosed by the surface until the net hydrophobicity of the protein is zero.

32. (Withdrawn) The system of claim 31, wherein the surface is chosen from the group consisting of an ellipsoid and a sphere.

33. (Original) An article of manufacture comprising:

a computer-readable medium having computer-readable code embodied thereon, the computer-readable code comprising:

a step to determine a hydrophobicity distribution of a protein; and

a step to shift the hydrophobicity distribution.

34. (Original) The article of manufacture of claim 33, wherein the computer-readable code further comprises, when shifting the hydrophobicity distribution, a step to shift the hydrophobicity distribution such that a total hydrophobicity of the protein is zero.

35. (Original) The article of manufacture of claim 34, wherein the computer-readable code further comprises a step to normalize the shifted hydrophobicity distribution, thereby causing a standard deviation of the shifted hydrophobicity distribution to be unity.

36. (Withdrawn) The article of manufacture of claim 35, wherein the computer-readable further comprises:

a step to determine, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

a step to determine a profile of the adjusted zero-order moment of hydrophobicity;

a step to determine a first distance of a maximum peak of a profile of the adjusted zero-order moment of hydrophobicity;

a step to determine a second distance at which the adjusted zero-order moment of hydrophobicity vanishes; and

a step to determine a ratio between the first and second distances.

37. (Original) The article of manufacture of claim 35, wherein the computer-readable code further comprises:

a step to determine, by using the shifted and normalized hydrophobicity distribution, an adjusted second-order moment of hydrophobicity;

a step to determine a profile of the adjusted second-order moment of hydrophobicity;

a step to determine a first distance at which a maximum peak of the profile of the adjusted second-order moment of hydrophobicity occurs;

a step to determine, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

a step to determine a second distance at which the adjusted zero-order moment of hydrophobicity vanishes; and

a step to determine a ratio between the first and second distances.

38. (Original) The article of manufacture of claim 33, wherein the computer-readable code further comprises, when determining a hydrophobicity distribution of a protein, a step to assign a hydrophobicity value to each of a plurality of residues of the protein.

39. (Withdrawn) An article of manufacture for spatially profiling proteins, comprising:

a computer-readable medium having computer-readable code embodied thereon, the computer-readable code comprising:

a) a step to determine a shifted and normalized hydrophobicity distribution for a protein;

b) a step to determine a centroid of the protein;

c) a step to determine, by using the shifted and normalized hydrophobicity distribution, an adjusted second-order moment of hydrophobicity; and

d) a step to determine a profile of the adjusted second-order moment of hydrophobicity.

40. (Withdrawn) The article of manufacture of claim 39, wherein the computer-readable code further comprises, when determining a profile of the adjusted second-order moment of hydrophobicity, a step to determine a first distance from the centroid at which the adjusted second-order moment of hydrophobicity is zero.

41. (Withdrawn) The article of manufacture of claim 40, wherein the computer-readable code further comprises:

e) a step to determine, by using the shifted and normalized hydrophobicity distribution, an adjusted zero-order moment of hydrophobicity;

f) a step to determine a second distance from the centroid at which the adjusted zero-order moment of hydrophobicity is zero; and

g) a step to determine a ratio between the first distance and the second distance.

42. (Withdrawn) The article of manufacture of claim 41, wherein:

the computer-readable code further comprises, when determining a first distance from the centroid at which the adjusted second-order moment of hydrophobicity is zero, a step to

determine a surface enclosing an interior volume wherein any larger of a surface will yield a negative adjusted second-order moment of hydrophobicity; and

the computer-readable code further comprises, when determining a second distance from the centroid at which the adjusted zero-order moment of hydrophobicity is zero, a step to increase the volume enclosed by the surface until the net hydrophobicity of the protein is zero.

43. (Withdrawn) The article of manufacture of claim 42, wherein the surface is chosen from the group consisting of an ellipsoid and a sphere.